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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,561	05/26/2006	Fengqi Ye	SHA 140NP	5972

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,561	YE ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *24* is/are allowed.

6)☒ Claim(s) *16-23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-23, 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baltzer or English, these in view of Xiong(2004).

Baltzer teaches the concept of a mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors; see title. These were formed in the exact same way applicants do, by esterifying both the β-lactam antibiotic and β-lactamase inhibitor to the same methylene group. The advantage of doing this over the alternative, a mixture of the two compounds, is set forth in the paragraph bridging pages 1183-1184, viz., that "both the antibiotic and the inhibitor are present simultaneously in appropriate balance at the site of the infection. This will not usually be the case when the two compounds are given as a combination .... because each drug in a combination will have its own individual profile with respect to rate of absorption, distribution and duration of action." This established that one of ordinary skill in the art would be well motivated to prepare the mutual prodrug rather than the combination of β-lactam antibiotic and β-lactamase inhibitor.

English has a very similar teaching. Again, sulbactam is linked in the same way to a penicillin. Page 346 notes the advantage to be expected: "There are several advantages

inherent to carboxyl-terminated double-ester prodrugs for oral delivery of pharmaceutical agents. The carboxyl moiety imparts improved water solubility, especially as the pH rises, as in transit from the stomach to the small intestine. It also provides improved prospects for isolation of crystalline solids as free acids or as sodium salts, thus creating options to improve formulation of oral delivery forms. Another advantage is the formation of potentially innocuous organic diacids as by products after hydrolysis to the parent drug in vivo. Clinically, these advantages can be translated to drugs that are more efficacious, safe, and convenient to use. In summary, the acid-termination concept of ester prodrug design has provided novel and effective delivery forms for the ß-lactamase inhibitor sulbactam. Similar application to other drugs in order to improve oral bioavailability, formulation, water solubility, and simultaneous byproduct formation is suggested." The "Similar application to other drugs" would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam.

The two examples of the primary reference, compounds 3 and 4, both employ sulbactam as the β-lactamase inhibitor. The β-lactam antibiotic in both cases is a penicillin. However, it would be obvious to use any "β-lactam antibiotic", as that is what the reference Baltzer teaches; again, see title and above cited paragraph. Likewise, English teaches "other drugs".

In Xiong(2004), note Table 2, which shows strong synergism between sulbactam and Cephalothin, Cefuroxime, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone. Note that cefuroxime is the second species in claim 16.

Some claims specify salts. This is not a patentable distinction, as β-lactams are routinely administered as salts, especially hydrochloride salts. Cefotiam hexetil

hydrochloride, Cefcapene pivoxil hydrochloride, Cefalexin hydrochloride, Cefepime hydrochloride, and Cefozopran hydrochloride are some examples of this.

The traverse is unpersuasive.

A. Applicants point to the age of the references (1980, 1989), and infers from this that "these compounds are difficult to obtain." The age of a reference, or that a given improvement appears after a long time lapse does not of itself prove that such change was unobvious. See In re Lechene, 125 USPQ 396; In re McCarn, 101 USPQ 411. The age says nothing about difficulty, and moreover, difficulty does not mean unobviousness.

B. Applicants next argue that "The present invention solves a technical problem which was desired to be solved for a long time but which had not be solved successfully." This is simply not true. Baltzer and English both made the mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors, and both formed them in the exact same way applicants do, by esterifying both the β-lactam antibiotic and β-lactamase inhibitor to the same methylene group. The only reason that these references don't anticipate is that neither used the exact permutation of β-lactam antibiotic and β-lactamase inhibitor. The solution of finding something better than a simple mixture of β-lactam antibiotic and β-lactamase inhibitor was already known. Thus, while applicants state that they "surprisingly successfully obtained...." Their product, there is no reason to see any of this as a surprise.

C. Applicants next point to the selection of "specific performance and reaction conditions". It's not at all clear what specifically applicants refer to, but even if true, that would only be relevant to method of manufacture claims. If applicants are saying that the sulbactam esters cannot be made except for methods which applicants invented, then such

an argument could overcome the rejection. However, applicants are not actually saying that, and its unclear how applicants could make such an argument, given that e.g. English certain seems to say that they can make the sulbactam esters.

D. Applicants state that their compounds have "an unexpected antibacterial effect". On what basis could the antibacterial effect possibly be considered unexpected?

E. Applicants argues "YR-1 and YR-2 have antibacterial activity in vitro which is nearly equal to that of the combination of parent drugs, and, for some bacterial strains, such as Proteus mirabilis, Bacillus preteus, Proteus morganii and Shigella flexneri, the antibacterial activities of YR-1 and YR-2 are veen better than that of the combination of parent drugs. Applicant respectfully submits that the above effects would not be obvious to one of ordinary skill in the art." This is unpersuasive for several reasons:

a. The testing is only done on derivatives of cefetamet and cefuroxime.

b. It is correct that in those 4 cases, the ester is better than the combination, for one or for both of cefetamet and cefuroxime. But in other cases, e.g. Pseudomonas aeruginosa 10124, Bacillus pneumoniae 46101, Bacillus aerogenes 45102, Citrobacter 48017, the results were the same. In some cases, one was the same, but for the other, the ester was actually worse, e.g. Candida eiferii 41002, Shigella sonnet 51081, Shigella bogdii 51313, and Diplococeus lanceolatus 31002. And in some cases, both were actually worse i.e. Staphylococcus aureus 26003, Salmonella enteritidis 50041, Salmonella typhi 50097, and E. coil 44102. This is perfectly normal --- some better, some the same, and some worse. In fact, taken as a whole, the ester was better than the combination in 6 cases, the same in 14, and worse in 12. That is more negative than positive.

c. Further, even in the cases where the ester is better, why is that unexpected? Both primary references teach that one expects the ester to be better than the physical combination.

Claim Objections

Claims 17-19, 22-23 recite salts, but salts are not provided for in claim 16. Adding salt to claim 16 will resolve the matter.

Claim 16 must end in a period.

Specification

Chinese characters must be removed from all tables; see e.g. top of page 9. The "acetdimethylamide" of example 9 and other examples is clearly wrong.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

5/5/2009